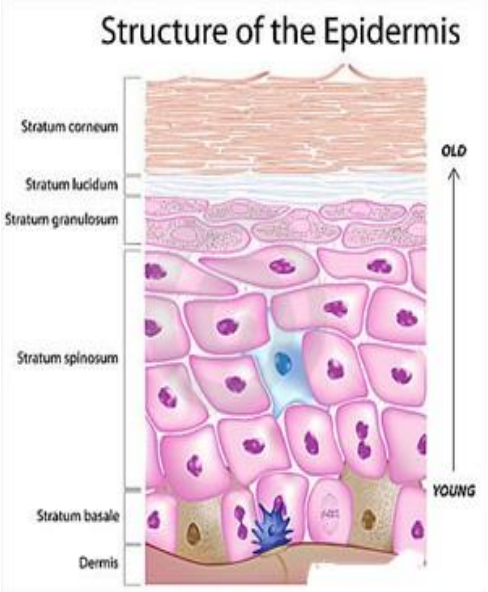
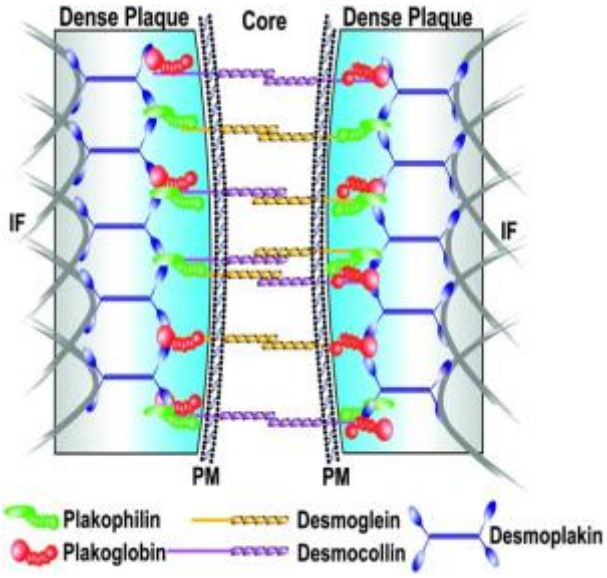
Bullous Diseases





Layers of the skin :

Basal cell layer:columnar , deep basophilic cytoplasm , dark staining , oval nucleus..it is attached to basement membrane zone.

Squamous (Prickle cell layer) :polyqonal keratinocytes connected togather with desmosome .

Granular cell layer: diamond shape ,contain keratohyaline granules + odland (lamellar granules).

Horny cell layer : flattened , dead , a nucleated eosinophilic.

DESMOSOME

Highly electron dense material containing proteins. Connect keratinocytes with each other. Consist of 3 groups of proteins:

1)**Intermediate Filaments** : Keratin 5 ,14

2)**Plaque** contain of plakin , Desmoplakin 1,2

3)**Core** Cadherins (Transmembrane Proteins) :desmoglein 1,3 + desmocolin 1,2

NB :Cadherin means Ca dependent adhesion molecules .

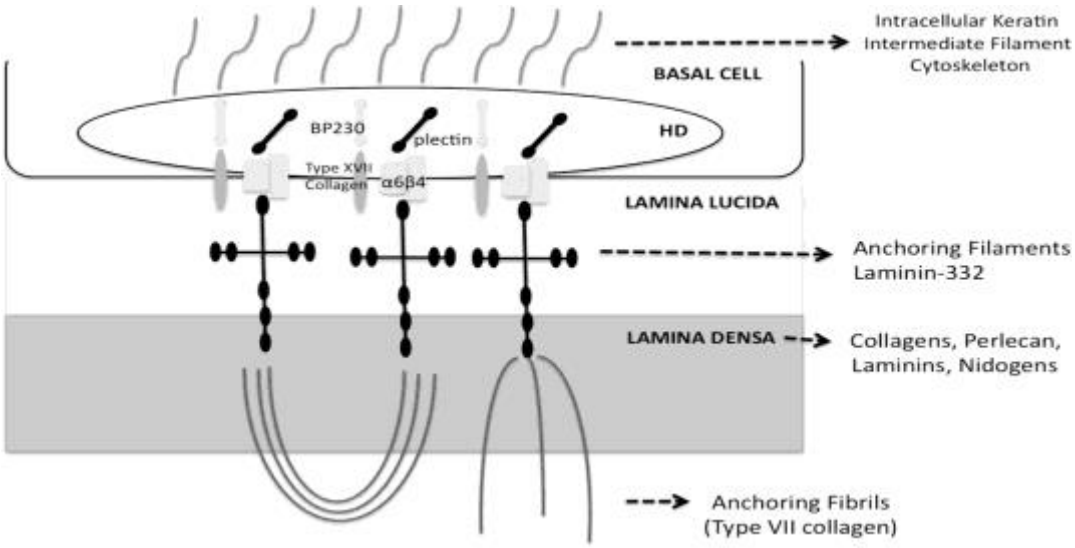
Dermo_epidermal Junction (DEJ) OR Basement membrane zone (BMZ)

***Function*:**

1)adhesion of dermis and epidermis. 2)mechanical support.

3)selective permeability, physical barrier.

4)Mesenchymal -epidermal interaction



Composition by electron microscope,

1)basal cell plasma membrane "hemidesmosome"HD,

1)**inner plaque** connect to KIF

2)**outer plaque** connected to plasma membrane

3)**sub basal dense plate**

2)lamina lucida;

Lucent area contain anchoring filaments from HD to LD

3)lamina densa;

Electron dense band

4)sublimina densa;

Fibrillar zone contain anchoring fibrils **not** filaments which may loop back to LD or inserted to electron dense plaque (anchoring plaque)

Molecular Components

1)Hemidesmosome,

Inner plaque : pectin (500KD) + BPAG1 (230KD)

Transmembrane components : BPAG2 (180 kd)

2)Lamina Lucida,

BPAG2 extracellular segment

B4 subunit(extracellular domain of α6B4 integrin) +L5 ,L1

Anchoring filament : IgA linear +laminin 5 +laminin 6

Laminin 5,6 connected together by disulfide bond

Uncein Fibronectin

3)Lamina densa,

1)collagen IV: Non Fibrillar collagen rod shaped with 4 domains ,it works as mesh like support of LD

2)Nidoqen : Small sulfated glycoprotein 150KD

3)Heparin sulfate proteoglycan : Glycoaminoglycan Regulate migration of charged cells throughout BM

4)Chondroitin-6-sulfate: the same as Heparin sulfate proteoglycan.

5)laminin 5,6.

4)Sublimina densa,

1)Anchoring fibrils : collagen **VII** ..... the target antigen is Bollous SLE

2) interstitial collagen : collagen **I,III** → papillary dermis

3)Microfilbrils : Fibrins+elastins

Pemphigus Vulgaris

Chronic autoimmune skin disease characterized by Intra_epidermal blister formation due to attacking of auto antibodies to desmosomal proteins.

Types,

Mucosal (mucosal ± minimal skin) → Target protein: Dg3

Mucocutaneous (mucosa+skin) → Target protein: Dg1+ Dg3

Desmoglien compensation theory :

In skin :Dg1 is expressed in upper epidermis , Dg3 in lower epidermis
In mucosa :Dg1 is expressed in lower level than Dg3

In skin Dg1 can compensate the defect of Dg3 so minimal affection or absent in skin but all the mucosa will be affected.

In Mucocutaneous PV affection of Dg1+ Dg3 both skin and mucous affected

Epidemiology:

Age →middle age Sex →male=female Race →more in Jewish

C/P:

Poor general condition due to mucosal affection→↓ decrease nutrition. Oral lesions are painful while Skin lesions are asymptomatic ± pruritic.

Skin lesion: Flaccid, thin wall ,fragile, easily ruptured blister→painful erosion that ooz and bleed easily →crust formation.

It is either on top of normal skin or erythemous Base.

The fluid is clear but may become haemorrhagic or turbid or pus.

Healing with hyperpigmentation + no scarring

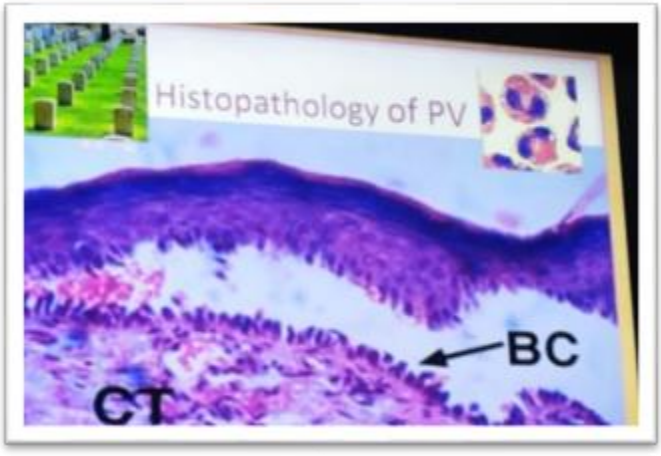
Nikolsky sign: firm sliding pressure or rubbing on normal skin → separation of epidermis and dermis →blister formation.

It indicate active disease ..It is positive in Toxic epidermal necrosis

AsbÖe_Hansen sign (indirect nikolsky):

Gentile pressure on intact bulla force the fluid to spread under the skin (spread of bulla)

histopathology



Intra _epidermal blister above the basal cell layer

Acantholysis (supra-basilar)

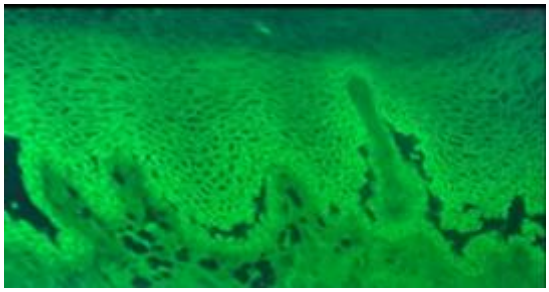
The basal cell layer still attached give tomb stone appearance

Inflammatory infiltrate (mainly eosinophilic)in cavity and dermis

Immuno Fluorescence;

Direct IF, perilesional skin why? dt consumption of complement in bulla.

Finding : IgG ± C3 on keratinocytes cell wall (inter cellular)



Indirect IF, serum blood sample + monkey esophagus .

Finding: circulating IgG

DD; ***Mucosal:*** Herpes stomatitis, LP, SLE , EM

Skin: other forms of pemphigus

Treatment;

1)Topical; CST , Antibiotic , Immunomodulators (tacrolimus)

2)Systemic; CST and other CST-SPARING immuno suppressive

A) cst prednisolone (1mg/kg/day)start with 60 mg/daily.

Intravenous pulse therapy :methyle prednisolone IV (1g/day for 3-5 days) in infusion very slowly 2-3 hours with good cardiac monitoring

B)CST-SPARING immuno suppressive:

Azathioprine...2_4mg/kg/day	S.E, Nqses /Myelosuppression
Cyclophosphamide...2_3g/day	S.E, Hgic cystitis +leucopenia
Methotrexate.(7.5_20mg/week)	S.E, N,V,hepatotoxicity, abortion
Cyclosporine 5mg/kg/day	S.E, HTN ,Nephrotoxicity

C)others : *High dose intravenous Immunoglobulins IvIg

*Plasmapheresis * Extra corporeal photopheresis ECP

Pemphigus vegetans

Vegetative form of PV or reactive pattern of PV

Subtypes: sever (blister) :Neumann

Mild (pustules):Hallopeau

C/P;

The same as PV + blisters become erosion then form fungoid vegetations or papillomatous proliferation

Site: intertriginous areas or scalp or face

Histopathology,

PV +papillomatous + Acanthosis+Intense inflammatory infiltrate (eosinophils + intra epidermal microabcess)

DD: ***BPH***

***B**lastomycosis like pyoderma

***P**yodermatitis-pyostomatitis vegetans

***p**emphigus Vegetans

***H**ailey-Hailey disease

Treatment; the same as PV

Pemphigus Foliaceus

*Less common than PV. *General good condition dt no oral lesions

Target Ag :Dsg1

Skin....superficial blister only cause Dsg3 will compensate the defect of Dsg1 in the lower epidermis only

Mucosa. ...no blisters cause Dsg3 will compensate the defect of Dsg1

Variants: **Localised**(P.erythematous) **Endemic** (Fogo selvangem)

C/P;

Skin lesions,burning + painful well demarcated scaly crusted erosion on erythematous base in seborrhoeic areas (scalp,face,upper trunk)

H/P;

Acantholysis in upper epidermis (with on adjacent to granular cell layer +intracavity inflammatory cells (neutrophil))

DD; *Other forms of Pemphigus *Bullous impetigo *S.D

Subcorneal pustular dermatosis (SCPD)

Subacute cutaneous lupus erythematosus

Prognosis; good and better than PV as commonly localized rare generalized (erythroderma)

Treatment; ***Localized,*** super potent topical CST

Active disease,systemic CST

If neutrophil is dominant in histopathology. .... Dapson

Senear usher syndrome P.erythematous. indistinguishable form of P.Foleceaus:

On face → LE like or Seborrhoeic dermatitis like

On trunk → sternal,interscapular areas similar as P.Foleceous

Paraneoplastic pemphigus

C/P;

Mucosa:sever mucosa affection .....erosion, ulceration, painful, progressive stomatitis +involvement of tongue

Skin:polymorphouspruritic skin erosion of:blisters, erosions, EM like lesions

Association: Solid tumours (Thymoma)

cancer(non hodgkin's lymphoma,chronic Lymphocytic Leukaemia)

In oral lesions : Dsg3 is present in all cases

In skin lesions: Dsg1 is present in 2/3 of cases

Histopathology; *supra basal acantholysis *keratinocyte Necrosis

*Vascular interface changes

DIF: IgG + complement deposition in intercellular space of ***keratinocytes(epidermis)*** ± granular linear deposition of C3 along BMZ

IIF; (Rat bladder) circulating IgG antibodies that bind to epithelial cell surface in 75% of cases

Target antigen :various desmosomal proteins, Dg3,Desmoplakin 1,2

Pathogenesis;

Tumors (containing plakins) → cytokine dysregulation →

Anti Dg3 IgG antibodies → Acantholysis →Disruption of cell membrane →exposure of plakins →Antiplakin IgG auto antibodies → inflammatory infiltrate →further acantholysis →keratinocytes Necrosis +blister formation

Treatment; Minor tumors excision Major tumours chemotherapy

Prednisolone 40_60mg /day alone or with cyclosporin

IgA Pemphigus

C/P; subcorneal pustular dermatosis _like .

More in axilla, groin

Pruritic ,flaccid vesicles +_pustules in an annular pattern with centeral crusting ..rare mucous membrane affection.

2 types;

	Intra epidermal neutrophilic dermatosis	***Subcorneal pustular dermatosis***
H/P	supra basal pustules + neutrophilic infiltrate + scanty acantholysis	subcorneal pustules +neutrophilic infiltrate +scanty acantholysis
DIF	IgA deposit in lower or intire epidermal cell surface	IgA deposit in upper epidermal cell surface
I IF	circulating IgA auto antibodies to epithelial cell surface (50%)	
Target antigen	Dsg3	Dsg1+Dsc1

Pathogenesis; Th2 → secret IL4,IL5 →stimulation of B-cells → produce IgA1 → bind to desmosome component → accumulation of neutrophils which bind to IgA-Fc receptor (CD89) →release protease enzymes →blister formation

Treatment; *Dapsoneis the drug of choice 100mg/day

*prednisone +puva

*systemic steroids

*Etretinate

Herpitiform Pemphigus

C/P; Dermatitis Herpitiform like

Pruritic ,erythematous (papules,vesicles, bulla, blisters) in Herpitiform pattern

Mucous membrane occasionally affected

H/P; Eosinophilic spongiosis ± Acantholysis

Intra-epidermal pustules filled with eosinophil or neutrophils

DIF; IgG deposit in upper or intire epidermal cell surface

IIF; circulating IgG auto antibodies

Target antigen; Dsg1 is more affected than Dsg3

Pathogenesis; IgG auto antibodies bind to Dsg1 → activation of keratinocyte → release IL8 → chemotactic to Neutrophils →release of protease from Neutrophils → blister formation .

Treatment; Dapsone100_300 alone or in combination with systematic steroids or Immuno suppressant

Bullous pemphigoid

Chronic auto immune disease characterized by subepidermal blistering with exacerbation and remission

Occurs in elderly 》 60 years but cab be juvenile (children)

More prevalent in pt: HLA DQB1,HLA-DRB1

Clinically;

1)Non bullous phase:

Mild to sever pruritus, eczematous, papular +_urticarial lesions that may last for several weeks or months.

2)Bullous phase:

Blisters :tense vesicle and bulla (1-4 cm) on normal or with erythematous skin ,contain clear fluid ,last for days, rupture leaving eroded and crusted areas

*Nikosky'sand Asboe-hansen sign are -ve

*symmetrical distribution mainly in flexural aspect of the limbs ,lower trunk, abdomen

*post inflammatory hyper/hypo pigmentation occur

*involvement of oral cavity in 10-30%of cases

*peripheral blood eosinophilia in 50% of cases

NB.Juvenile Bp: clinically similar to BP but differ in

1)start in acral sites then generalised

2)spontaneous remit in 5 years so no need for over treatment to avoid medical side effect.

Associations;

1)Autoimmune disease : SLE ,Rheumatoid A

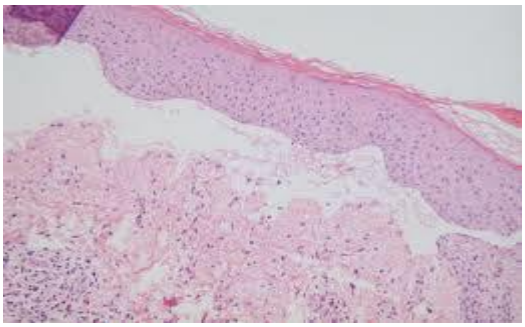
2)Drugs (it a six, pencillamine) ,captopril, NSAID

3)PUVA,UVB

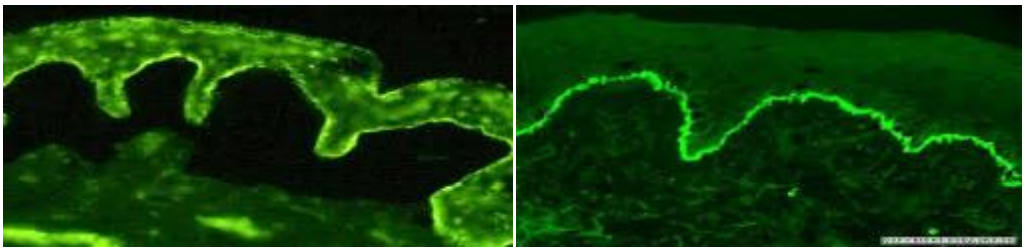
4)internal malignancy (paraneoplastic syndrome),cancer Git,Bladder,Renal

H/P;

Sub-epidermal bulla with marked eosinophilic infiltrate (cell rich BP) and rarely few infiltrate (cell poor BP).



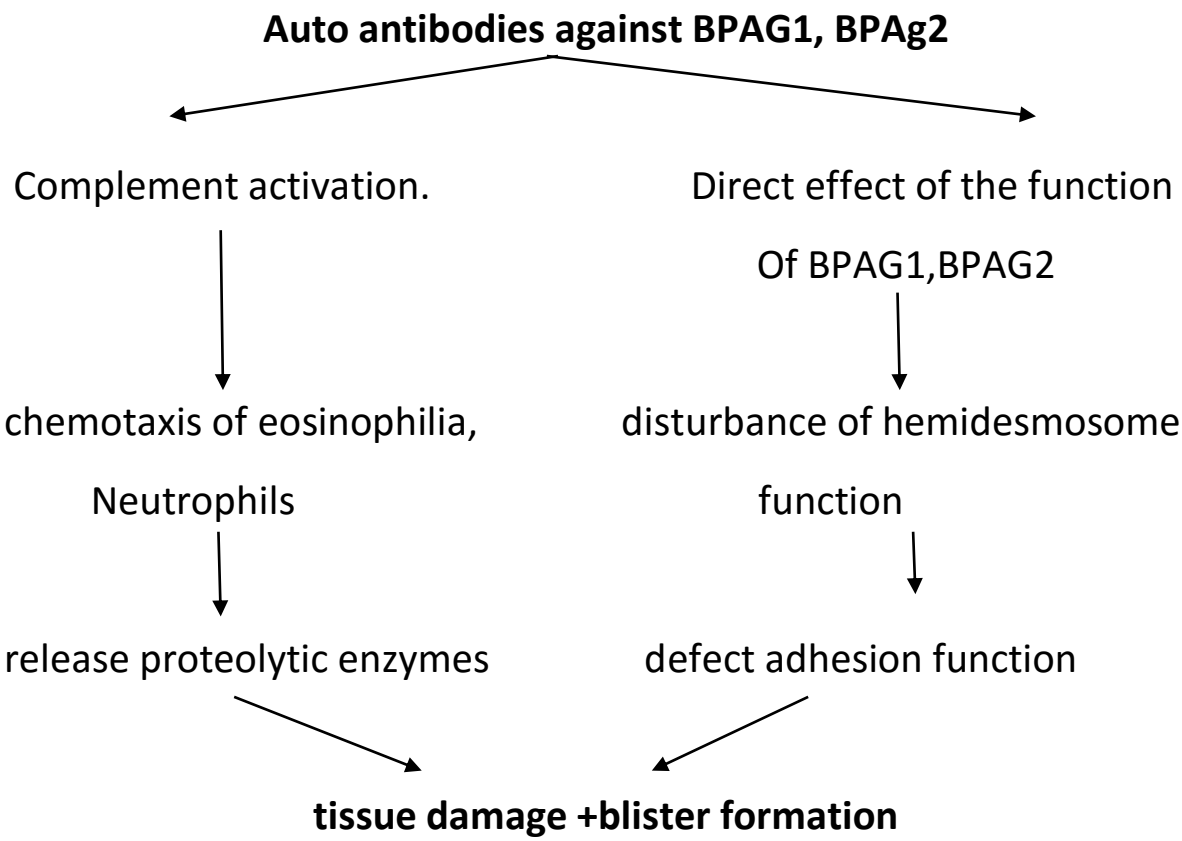
DIF; perilesional skin:shows linear deposition of IgG and or C3 complement along the DEJ within the lamina lucida in almost all patients.



IIF; circulating IgG auto antibodies (IgG1,IgG4)directed against BP antigen located in DEJ in 80% of patients

Target antigen:BPAg1 (230KD)&BPAg2 (180 KD)

Pathogenesis;



Treatment;

1)potent topical CST in localised lesions

2)steroid systemic in low dose (40-60mg/day)/6months

3)Immunosuppressive (Azathioprine)

4)Anti-inflammatory drugs (tetracycline 800 (1×4)),Dapsone(50-100)(1×4)

Cicatrical Pemphigoid

Rare chronic auto immune disease involving mucous membrane +- skin ,especially (oral,conjunctival M.M)result in scarring

Middle /old age (50-80 years) with chronic course.

Types;

	Group 1 (antilaminin)	***Group 2 (Ocular)***	***Group 3***	***Group 4***
Target Antigen	laminin (322) L5, laminin (311) L6	B4 subunit of α6B4 Integrin	BPAG2 180KD	unclear but may be proteins of epithelial BM
Involvement	Associated with solid tumors of GIT,lung. Tumours develop 2 years after skin lesions	pure or predominant ocular involvement	affect skin +M.M	affect M.M without skin involvment.

Clinical symptoms;

1)**Ocular symptoms** :

→Conjunctivitis, entropion. →corneal neovascularization scarring

→Trichiasis (def:abnormal positioned eye lash)

→Symblepharon :fusion of palpebral, bulbar conjunctiva
→blindness

2)Skin lesions (25-30%);

Common sites :scalp,neck,face,upper trunk

Lesions : erythematous plaque, recurrent blister formation (erosion),limited number. **NB** Scaring alopecia.....if lesion in scalp

H/P;

DIF; similar to BP

IIF; +ve in 20% of cases

Binding to the roof ***ie*** epidermal side of the split

In type 1 .....Binding to dermal side of the split

DD;

1)linear IgA disease 2)Subepidermal bullous disease

3)Anti-D2oo pemphigus 4)Bullous LE 5)EBA

Treatment;

1)local.....VIP

Skin Lesions. ...topical steroid

Oral lesions. ....topical steroids :mouth wash,oral gel, oclusiveBase

Abcs mouth wash , Good hygiene

2)systemic..

1st line.....dapsone 50/150mg/d

2nd line.....cyclophosphamide (1-2 mg/kg/day)

It is the drug of choice for rapidly progressive ocular lesions+-steroids

3rd line.....Immunosuppressive :Azothioprine , Mycophenolatemofetil , others:cyclo spine, tacrolimus (tetracycline)

3)Surgical. .after medical therapy for sever scars in eye,larynx,oesophagus

Dermatitis Herpetiform

(DH)duhring disease

Chronic auto-immune bullous disease

Increase Incidence with HLA-DQ2, HLA-B8

Diagnosis;

1)C/P:

Sever pruritus, symmetrical, polymorphic,erythematous,plaques, vesicles, urticarial wheels

Sites: extensor surfaces of limbs, shoulders, buttocks

Healing with scar +pigmentation

History of ingestion of **gluten** or **iodide** diet

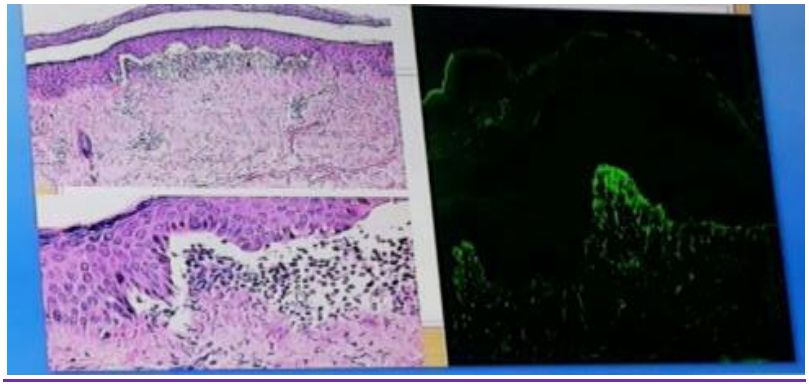
2)investigation;

H/P;

Biopsy. ...perilesional skin

Subepidermal vesicle , Papillary neutrophilic microabcessin dermal papilla, dermal perivascular neutrophilic infiltrate with nuclear dust

EM. ..... lamina lucida skin cleavage.



DIF; perilesional skin....granular IgA (IgA1 class)deposition on dermal papilla

Serum Findings;

IIF :circulating ANTI-BMZ Antibodies usually –ve.

Auto-Ag :epidermal transglutaminase & tissue transglutaminase

Auto-Ab :Antireticulin,Anti-thyroid Ab ,Anti-gliadin About,

IgA immune complex

Association;

1)Gluten sensitive entropathy,

Is found in 90% of patients with dermatitis Herpetiform Gluten is found in wheat,Rye and not found in rice or corn **Gliadin:**the soluble fraction is the antigenic component

2)Defective mucosal barriers is found in almost all patients

3)DM,Thyroiddisease,Internal malignancy :lymphoma

Pathogenesis;

Defectivemucosal barrier→passage of Gluten macromolecules→reach lamina propria→activation of immune response→IgA1 antibody →immune complex released in circulation →deposited in dermal papilla →release of chemo-attractants →Neutrophils attracted to upper dermis→release of pruritus substance +proteolytic enzymes → L.L separation +vesicle formation.

Treatment;

1st line...Dapsone(100-200mg/day)

Therapeutic test ....significant response in 1st 48hours

2nd line...sulfapyridine(1-2 gm/day)

3)modify life style.: very important

Gluten free diet help in

1) decrease skin lesions

2)less Dapsone take

3)protect the patient from lymphoma

D.D; IGA bullous dermatosis

Epidermolysis Bullosa Acquisita (EBA)

Rare, acquired subepidermal bullous disease .The defect in type 7 collagen (the main component of anchoring fibrils of DEJ) main in adult ,child ,no family history.

Clinically ; 3 types

(1)Non-inflammatoryMechanobullous,

Acral blisters that heal with atrophic scar, Milia, hypo/hyperpigmentation

Found in trauma areas : elbow,knee,dorsum of hand

Acral involvement may be mutilating. .....mitten deformity of digits+nail dystrophy +complete nail loss +scalp involvement in 20% of cases

(2)Inflammatory BP-LIKE,

Wide spread bulla,vesicles in intertreginousareas,Flexure, no miliaor atrophic scar, mucous membrane like BP,scaring alopecia

It is undistinguished with BP or Mucous membrane cicatricialP

(3)Mucosal disease,

Affect M.M exclusive

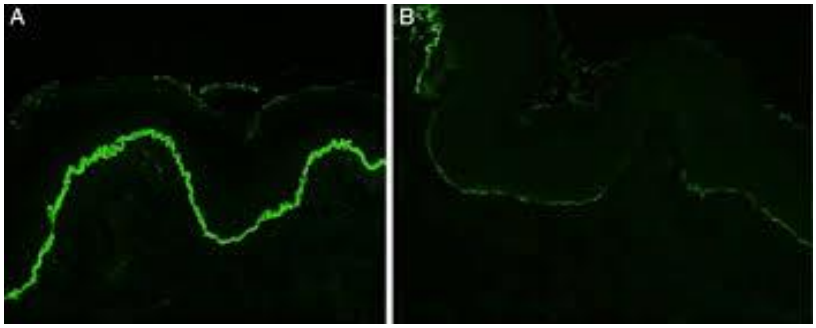
Oral manifestation :ulcers,bulla,desquamative gingivitis

Nasopharynx : larynx,analmucosa may be involved .

NB all types are *Associated with inflammatory bowel disease*

H/P;subepidermal bulla ,just below lamina densa with predominant neutrophils

DIF; Linear BMZ of C3,IgG



IIF; IgG against BMZ

Split skin binding ;dermal side (floor)

Antigen; Type collagen ***VII***

Pathogenesis; Recognition of type 7 collagen as foreign body (Antigen) → Autoantibody formation (IgG) → Ab bind to DEJ in sublamina densa →complement fixation → chemotaxis of PMNL →proteolytic enzymes →SLD separation → blister formation

Treatment;

1)Steroid 40-60 mg/day

2)Dapson

3)Immunosuppressive:(Azathioprine, Methotrexate,Mycophenolate)

Subcorneal pustular dermatosis

Rare benign disease characterized by chronic relapsing sterile pustular eruption

Age 40-50 years

Female:male 4:1

C/P;

Chronic relapsing disorder with sterile pustules in annular pattern

Site:Abdomen ,Axilla ,groin

Pus accumulation in lower half of pustules

Realing with superficial crust then brown pigmentation

THE FACE AND MUCOUS MEMBRANE NEVER AFFECTED

Association; IgA gammopathy,pyoderma gangrenosum,inflammatory bowel disease

H/P;

1)Subcornealneutrophiliswith 2ry few acantholyticcells are seen in the Base of pustules

2)Dilated capillaries +perivascular neutrophilic infiltrate in underlying dermis

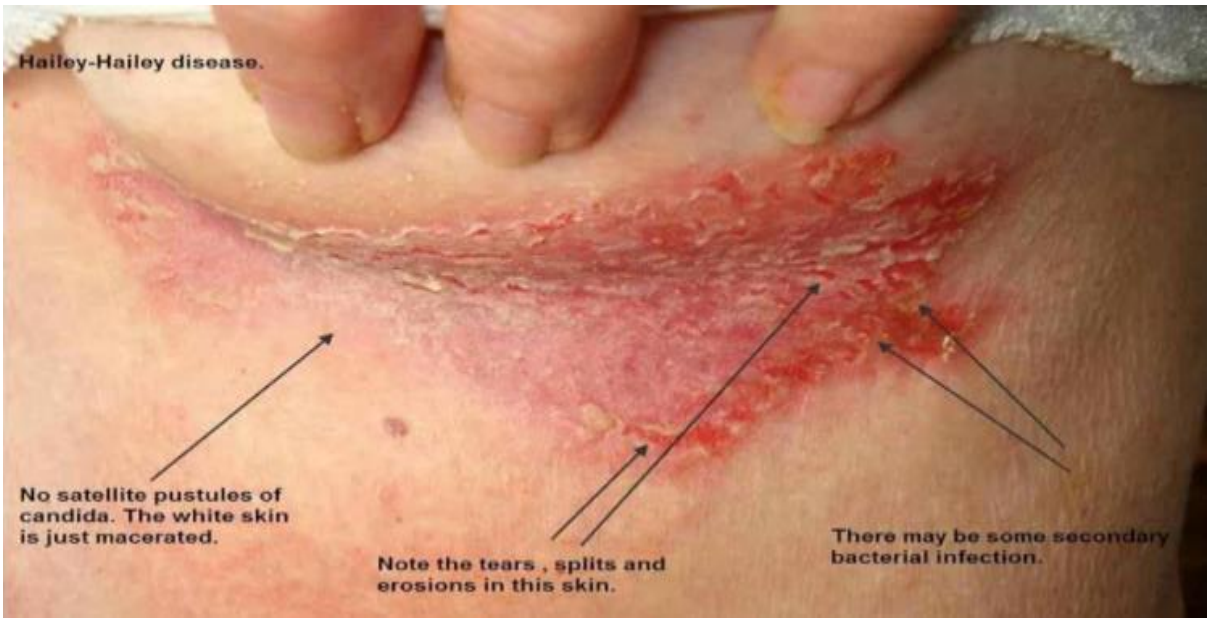
Treatment; Dapson 50-150mg

Sulfapyridine1-2 gm/day

Hailey-Hailey disease

AD disorder with +ve family history (2/3 patients) ,the age of onset 15-25 years

C/P;



Recurrent small flaccid vesicle on erythematous Base with peripheral extension give circinatebattern, bruritus and burning is common, healing with hyperpigmentation ,mucosal affection is rare.

SITE; side,nape of neck,axilla, groin

Nail changes; asymptomatic or longtudinal band (longtudinalleukonychia)

Exacerbating factors; heat, trauma, infection (bacteria , candida)

Pathogenesis; AD. Caused by mutation of ATP2C1 gene result in dysfunction of Golgi -associated caATPasethus interferening with intracellular ca signaling

Complications;

1)Infection : 2ry bacterial , fungal , viral (colonization)

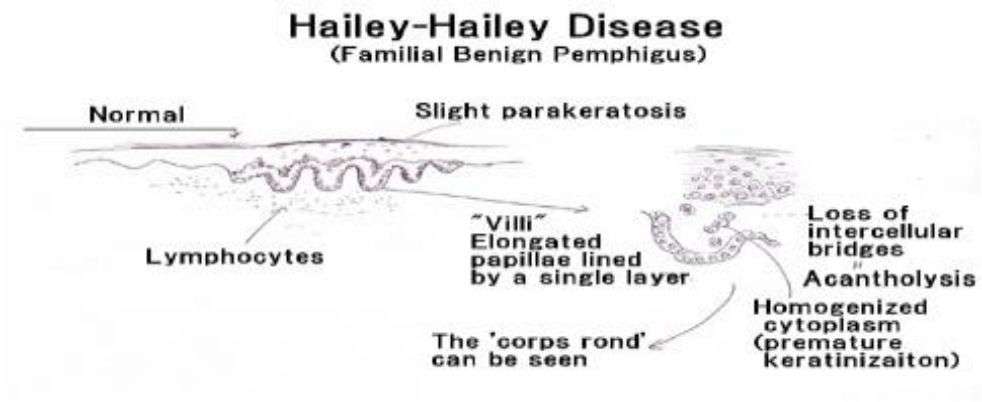
2)Malignancy; SCC

Clinical subtypes;

Segmental type 1 : unilateral lesions along Blaschko's lines

Segmental type 2 : Generalized, have a linear streak with increased severity , earlier onset.

H/P;



Supra-basal lacuna → vesicle, bullae

Villi protrude upward into the bullae

Acantholysis: extensive but less sever than PV.

few intercellular bridges remain. ....**dilapidated brickwall**

few dyskeratotic cells.....crops and rods

DIF, IIF; -ve because it is geno bullous not immuno bullous

Treatment; ♦Dapson (50-150 mg/day) the drug of choice

♦sulfapyridine. ...alternative ♦colchicine

♦photo therapy : BBUVB , NBUVB , PUVA , RE-PUVA

Steroids are ineffective even if taken in large doses.